REMARKS

Claims 1-8, 10-43, 45-51, 53, 55, and 57-59 were pending prior to this Response with claims 46-51, 53, 55, and 57-59 having been withdrawn. By the present communication, claim 60 has been added, claims 1-6, 7, 8, 10, 11, 20, 21, 23, 24, 26, 28, 29, 31-39, 41, 42, and 45 have been amended to define Applicants' invention with greater particularity, and claims 12-19 and 40 have been canceled. Support for the amended claims may be found throughout the specification, *e.g.*, at paragraphs [0035], [0027]-[0028], [0033], [0071], [0073]-[0074], [0077], [0079]-[0081], [0087], [0099]-[0103] and claims as originally filed. Accordingly, upon entry of the present amendment, claims 1-8, 10, 11, 20-39, 41-43, 45, and 60 will be pending and under consideration in this application.

Priority

The Office Action has acknowledged Applicants' foreign priority claim to application 04090072.2, filed in European Patent Office on February 27,2004 and application 04090175.3, filed in United Kingdom Patent Office on May 6,2004 but notes that certified copies of the same have not been filed pursuant to 35 U.S.C.119(b). Accordingly, Applicants have ordered certified copies of the aforementioned foreign applications, which will be submitted to the Office immediately upon arrival.

Objection to the Claims

Claims 2-4, 8, 7, 12-18, 20, 21, 23, 24, 26, 28, 29, 31, 33, 35, 40, and 42 have been objected to on the basis of allegedly containing various informalities. Without acquiescing to the reasoning offered by the Office Action, and in order to expedite prosecution of the instant application, Applicants have amended claims 2-4, 8, 7, 12-18, 20, 21, 23, 24, 26, 28, 29, 31, 33, 35, 40, and 42 as suggested by the Examiner. Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112, 1st Paragraph (Enablement)

Applicants respectfully traverse the rejection of claims 1-4, 7, 8, 10-26, 28-31, 33-37, 39-42, and 45 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

It is well known that to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without *undue* experimentation. *See, Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569,224 USPQ 409 (1984). This sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." *In re Anderson,* 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocci* et al., 469 USPQ 367 (CCPA 1971). Moreover, as explained in *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976), some experimentation is acceptable. MPEP §2164.01 explains, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." No showing has been made that the work required, as well as any experimentation that may occur along the way, would be anything but routine. In summary, MPEP §2164.01(c) states that "[i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. §112 is satisfied."

Further, because "it is manifestly impracticable for an [a]pplicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz,* 124 USPQ 449,502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a

reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11,24 USPQ 26,30 (1935). Thus, even though the application provides support for the claimed subject matter, there is no requirement for disclosure of every single species within a genus. Applicants are entitled to claims that are commensurate in scope not only with what Applicants have specifically exemplified, but also with that which one of skill in the art could obtain by virtue of that which the Applicants have disclosed. Furthermore, citing *In re Angstadt*, 537 F.2d at 503, 190 U.S.P.Q. at 218 "in an unpredictable art, disclosure is not required of a test with every species covered by a claim..."

Without acquiescing to the reasoning provided by the Office and in order to expedite prosecution, Applicants have amended independent claim 1 to recite "[a] method for detecting a colon cell proliferative disorder in a human subject comprising:

a) obtaining from the subject a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, or isolated blood cells;

b) contacting the genomic DNA with at least one reagent that distinguishes between methylated and non-methylated CpG dinucleotide sequences within ALX4 gene sequence (SEQ ID NO:5); and

c) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder." Applicants point to paragraph [0028] of the specification, which describes how the presence or absence of methylation correlates to colon cell proliferative disorders. Additionally, paragraphs [0251], [0258]-[0262] of Example 1 describe the determination of the methylation status of the ALX 4 gene and its utility in the detection of colorectal cancer (CRC).

The Office Action asserts with regard to claims 1, 2, and 8 that "age-related methylation is a common event in human tissue [and] it is unclear how the presence of methylated CpG dinucleotides within at least one of any target region of the genomic DNA isolated from blood plasma, blood serum, whole blood, isolated blood cells, or cells isolated from the blood obtained from a subject must indicate the presence of a colon cell proliferative disorder such as colon cancer in the subject and cannot indicate that the subject such as a human is a subject with old age," citing

Seminars in Cancer Biology, 9, 349-357, 1999 in support of its position. Applicants respectfully submit that the cited reference indicates (see Abstract) "in colorectal cancer, there appears to be two types of methylation that are associated with cancer progression: type A (for age-related) methylation, and type C (for cancer specific methylation). Initially, type A methylation arises as a function of age [but] result[s] in a predisposition state that precedes tumor formation in the colon." When taken in context, the reference cited by the Office does not raise a question of distinguishing between age-related methylation and methylation associated with colorectal cancer given that all types of CpG methylation described by the reference have a direct correlation with cancer progression. The reference merely states that type A methylation is *initially* age-dependent but precedes tumor formation in the colon. Furthermore, paragraph [0265] in Example 1 of the results section of the specification states "[s]pecificity of the panel in asymptomatic individuals over 50 years of age was 91%," wherein specificity is described at paragraph [0018] of the specification as follows: "[s]pecificity, on the other hand, is a measure of a test's ability to identify accurately patients who are free of the disease state. A test having poor specificity produces a high rate of false positives, *i.e.,* individuals who are falsely identified as having the disease." Therefore, the data contained specification clearly indicate that false positives *i.e.*, in practice there was a low incidence of subjects prone to age-related methylation and presenting aberrant methylation but not having a colon cell proliferative disorder.

The Office Action states: "claims 3, 4, and 7 do not indicate what kind of differences exist in the expression levels of the ALX 4 gene or gene sequences thereof among colon cell proliferative disorders in a subject and the specification does not show what kind of differences exist in mRNA expression levels of the ALX 4 gene." Without acquiescing to the rationale provided by the Office, and in order to place the claims in better condition for allowance, Applicants have amended independent claim 3 to recite "[a] method for detecting a colon cell proliferative disorder in a human subject comprising: determining the expression levels of ALX 4 gene (SEQ ID NO:5) or gene sequences thereof, in a sample from the subject comprising colon cells, colon fluid, stool, or colon tissue; and comparing the ALX 4 gene (SEQ ID NO:5) expression level in the sample with the expression level from a subject not having a colon cell proliferative disorder, wherein reduced expression of the ALX 4 gene (SEQ ID NO:5) in the

sample as compared with the sample from the subject not having a colon cell proliferative disorder is indicative of a colon cell proliferative disorder. Thus, as amended, claim 3 identifies the nature of differences in the expression levels of the ALX 4 among colon cell proliferative disorders in a subject. Additionally, Applicants point to paragraph [0027] of the specification, which further describes that "under-expression...is indicative of the presence of [cell proliferative disorders]." Moreover, the specification *e.g.*, at paragraphs [0105]-[0109] provides ample support for the detection of colon proliferative disorders and describes the correlation between mRNA expression levels and colorectal cell proliferative disorders, as well as methods for detecting aberrant mRNA expression for the purpose of detecting colorectal cancer.

The Office Action further asserts that claims 8, 10-17, 19-26, 28-31, 33-37, and 39-42 "do not indicate what kind of differences exist in methylated CpG dinucleotides within at least one target region of the genomic DNA isolated from a biological sample among different cell proliferative disorders..." Without acquiescing to the rationale provided by the Office, and in order to expedite prosecution, Applicants have amended independent claims 8 and 20 to recite "[a] method for detecting a colon cell proliferative disorder in a human subject comprising... d) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder." The amendments to independent claims 8 and 20 establish the differences that exist in methylated CpG nucleotides with respect to the detection of a colon cell proliferative disorder. As discussed above, support for the amendments may be found at paragraph [0028] of the specification as originally filed, which describes how the presence or absence of methylation correlates to a colon cell proliferative disorder and additionally at paragraphs [0251], [0258]-[0262], among others. Claims 12-17 and 19 have been canceled without prejudice or disclaimer, rendering the rejection moot with respect to these claims.

The Office Action states that claim 45 "does not indicate what kind of differences exist in cleavage fragments among colon cell proliferative disorders." While not acquiescing to the

reasoning provided by the Action, Applicants have amended independent claim 45 to recite "[a] method for detecting colon cell proliferative disorders in a human subject comprising:

a) obtaining, from the subject, a biological sample comprising genomic DNA from blood plasma, blood serum, whole blood, isolated blood cells, colon cells, colon fluid, stool, or colon tissue;

b) extracting, or otherwise isolating the genomic DNA;

c) contacting the genomic DNA of b), or a fragment thereof, comprising at least 16 contiguous nucleotides of SEQ ID NO:5 and sequences that hybridize under stringent conditions thereto, with one or more methylation-sensitive restriction enzymes, wherein the genomic DNA is either cleaved thereby to produce cleavage fragments, or not cleaved thereby;

d) determining the CpG methylation status of SEQ ID NO:5, or an average, or a value reflecting an average methylation status of a plurality of CpG dinucleotides target CpG dinucleotide sequences within SEQ ID NO:5; and

e) comparing the CpG methylation status in the sample with the CpG methylation status from a subject not having a colon cell proliferative disorder, wherein a difference in the CpG methylation status is indicative of a colon cell proliferative disorder. Thus, claim 45 does not recite differences in cleavage fragments among cell proliferative disorders.

Furthermore, Applicants respectfully submit that the use of methylation-specific primers (MSP) for the determination of methylation status is a technique that is known in the art and described in the specification at *e.g.*, paragraphs [0056] and [0180].

The Office Action asserts that if the primers in claim 21 or nucleic acid molecule in claims 39-42 are "TTTTTTTTTT" from SEQ ID NOS: 313 and 429, "which can hybridize polyA sequence of many different mRNAs then a "specific hybridization complex for human ALX 4 gene" cannot be formed. Applicants respectfully submit that amplification of bisulfite converted DNA i.e., SEQ ID NOS: 313 and 429 is performed "using primers specific for the CpG islands of interest" (see paragraph [0081]), thus a skilled artisan would not select a primer with the sequence "TTTTTTTTTT" for this purpose. Moreover, CpG sites are regions of DNA

where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases along its length. Claims 39-42 depend from claim 21, which in turn depends from claim 8, wherein claim 8 includes the following limitation with respect to the 9 contiguous nucleotide segment: "and the contiguous nucleotides comprise at least one CpG dinucleotide sequence." Thus, it is axiomatic that a nucleic acid or primer that would hybridize a 9 contiguous nucleic acid segment of interest of SEQ ID NOS: 313 and 429 would not be "TTTTTTTTTT." In view of the foregoing discussion, Applicants respectfully request withdrawal and reconsideration of the rejection.

Rejection under 35 U.S.C. §112, 2nd Paragraph

Applicants respectfully traverse the rejection of claims 1-4, 7, 8, 10-26, 28-31, 33-37, 39-42, and 45 under 35 U.S.C. §112, second paragraph on the ground of alleged indefiniteness. Specifically, the Office Action asserts that claims 1, 4, 8, and 45 are "vague and indefinite" because they include the following language: "detecting and distinguishing between or among colon cell proliferative disorders" in the preamble. Applicants respectfully submit that the Office Action contains an apparent typographical error on page 13 at item # 21 in view of the fact that previously presented claim 3, and not claim 4, contains the "detecting and distinguishing" phrase. While not acquiescing to the rationale provided by the Office, and in order to further prosecution of the instant application, Applicants have amended independent claims 1, 3, 8, 20, and 45 such that they no longer recite "detecting and distinguishing between or among" and now define the Applicants' invention with greater clarity.

The Office Action also asserts that claims 1, 7, 8, 19, and 20 lack sufficient antecedent basis for various phrases and terms. Without acquiescing to the reasoning offered by the Office, and in order to further prosecution of the instant application, Applicants have canceled claim 19, rendering the rejection moot with respect to this claim, and amended claims 1, 7, 8, and 20 accordingly.

The Office Action further asserts that claims 10-18, 21, 23, 34, 37, 39, and 41 are "vague and indefinite" for miscellaneous reasons. Without acquiescing to the rationale provided by the

Office, and in order to further prosecution of the instant application, Applicants have canceled claims 12-18, rendering the rejection moot with respect to these claims, and amended claims 7, 10, 11, 21, 23, 34, 37, 39, and 41 in accordance with the Action's request for clarification with regard to these claims.

The Action contends that claims 39-42 are indefinite and states that "it is unclear that the at least one nucleic acid molecule or peptide nucleic acid molecule hybridizes to what."

Applicants point to paragraphs [0074], [0076], [0081], [0089], [0092], and [0146], which describe in detail the various procedures for detecting CpG methylation status. It is art-recognized that such methods entail probe hybridization or labeled hybridization probes. Moreover, paragraph [0146] states: "hybridization of an oligonucleotide probe to a nucleic acid sample." Thus, a skilled artisan, in view of the description in the specification and in possession of general knowledge in the art, would understand the meaning of the hybridization language in claims 39-42 and interpret the same to mean hybridization of nucleic acid molecules or peptide nucleic acid molecules to the sample of interest for the express purpose of determining CpG methylation status. Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and the remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this case.

No fees are believed to be due in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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